UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Date: May 14, 2009

SUBJECT: **Metam Sodium**: Second Report of the Cancer Assessment Review Committee

PC Code: 039003
Decision No.: N/A
Petition No.: N/A
Risk Assessment Type: Cancer Assessment
TXR No.: 0055107
MRID No.: N/A

DP Barcode: N/A
Registration No.: N/A
Regulatory Action: N/A
Case No.: N/A
CAS No.:
40 CFR: N/A

FROM: Jessica Kidwell, Executive Secretary Jessica Kidwell
Cancer Assessment Review Committee
Health Effects Division (7509P)

THROUGH: Jess Rowland, Co-chair
Cancer Assessment Review Committee
Health Effects Division (7509P)

TO: Judy Facey, Toxicologist
Risk Assessment Branch VI, Health Effects Division(7509P)

Karen Santora, RM52
Reregistration Branch 2, Special Review and Reregistration Division

The Cancer Assessment Review Committee met on February 25, 2009 to re-evaluate the carcinogenic potential of Metam Sodium. Attached please find the Final Cancer Assessment Document.

Rec'd in RRB 5/27/2009

CANCER ASSESSMENT DOCUMENT

SECOND EVALUATION OF THE CARCINOGENIC POTENTIAL OF

Metam Sodium

PC Code 039003

Final
May 14, 2009

CANCER ASSESSMENT REVIEW COMMITTEE
HEALTH EFFECTS DIVISION
OFFICE OF PESTICIDE PROGRAMS

METAM SODIUM CANCER ASSESSMENT DOCUMENT FINAL

DATA PRESENTATION: Judy Facey
Judy Facey, Toxicologist

DOCUMENT PREPARATION: Jessica Kidwell
Jessica Kidwell, Executive Secretary

COMMITTEE MEMBERS IN ATTENDANCE: (Signature indicates concurrence with the assessment unless otherwise noted.)

Lori Brunsman, Statistician	Lori L. Brunsman
Ray Kent	Jessica Ryman for Ray Kent
Nancy McCarroll	Nancy McCarroll
Karlyn Middleton	Karlyn Middleton
Rob Mitkus	Robert J. Mitkus
Esther Rinde	Esther Rinde
Jess Rowland, Co-Chair	Jess Rowland

NON-COMMITTEE MEMBERS IN ATTENDANCE: (Signature indicates concurrence with the pathology report)

John Pletcher, Consulting Pathologist See attached sheet

OTHER ATTENDEES: Jessica Ryman (HED/RAB IV), P.V. Shah (RD)

DATA PRESENTATION: ____________________
Judy Facey, Toxicologist

DOCUMENT PREPARATION: ____________________
Jessica Kidwell, Executive Secretary

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NON-COMMITTEE MEMBERS IN ATTENDANCE: (Signature indicates concurrence with the pathology report)

John Pletcher, Consulting Pathologist ____________________

OTHER ATTENDEES: Jessica Ryman (HED/RAB IV), P.V. Shah (RD)

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EXECUTIVE SUMMARY

On February 25, 2009 the Health Effects Division's (HED's) Cancer Assessment Review Committee (CARC) met to re-evaluate the carcinogenic potential of metam sodium. This was the second carcinogenicity evaluation of metam sodium. The first meeting was conducted by the Carcinogenicity Peer Review Committee (CPRC) on March 1, 1995.

At the 1995 meeting, the CPRC concluded that metam sodium should be classified as a *Group B2 - probable human carcinogen*, based on statistically significant increases in malignant angiosarcomas in both sexes of the CD-1 mouse, supported by a similar tumor type (malignant hemangiosarcomas) in male Wistar rats (HED Document No. 011541). The CPRC recommended that for the purpose of risk characterization, a low dose extrapolation model be applied to the animal data for the quantification of human risk (Q_1*), based on the total incidence of angiosarcomas in male mice, at all sites combined. In March 1995, an estimated unit risk, Q_1* (mg/kg/day), of 1.98×10^{-1} in human equivalents, was calculated for metam sodium based upon angiosarcoma rates in male mice (Memo, B. Fisher, 3/10/95, TXR No. 0012954).

Since that time the registrant has submitted a Pathology Working Group (PWG) review of hemangiomatous lesions in the male Wistar rats (MRID 47067501) from the two year chronic toxicity/carcinogenicity study of metam sodium (MRID 43275802). They requested that the CARC re-evaluate the cancer classification of metam sodium based on the PWG review and according to the descriptors in the 2005 Guidelines for Carcinogen Risk Assessment.

This CARC report is a stand alone document that replaces the previous CPRC report (HED Document No. 011541).

The CARC considered the following for a weight-of-evidence determination of the carcinogenic potential of metam sodium:

Carcinogenicity

Mouse

- Administration of metam sodium in the drinking water to CD-1 male mice resulted in a significant increasing trend and a significant difference in the pair-wise comparison of the high dose with the control for angiosarcomas all sites combined, both at ($p<0.01$). For combined angiomas and angiosarcomas, there was a significant increasing trend as well as a significant difference in the pair-wise comparison of the high dose group with the controls, both at ($p<0.01$), and both of which were driven by the angiosarcomas. In female mice, there was a significant increasing trend for angiosarcomas at all sites combined ($p<0.01$). For female combined angiomas and angiosarcomas, there was a significant increasing trend at $p<0.01$, driven by the angiosarcomas. **Therefore, the CARC considered the angiosarcomas in male and female mice to be treatment-related.**

- *Adequacy of Dosing*: Dosing in the mouse study was considered to be adequate at the high dose for assessing the carcinogenic potential of metam sodium in both sexes. This was based on decreased body weight gain, increased liver weight, and fat vacuolation in the liver in males, as well as urinary bladder histopathology in both sexes.

Rat

- The PWG review of the hemangiomatous tumors in Wistar rats concluded that the incidences of benign and malignant hemagiomatous tumors were not treatment-related. The CARC concurred with this decision.
- *Adequacy of Dosing:* The high dose was considered adequate for testing the carcinogenic potential of metam sodium in rats, based on the decreases in body weight gain, food efficiency, and macroscopic and microscopic pathology observed in both sexes in this study.

Mutagenicity

There is no mutagenic concern for metam sodium.

Structure Activity Relationship

Metam sodium, dazomet and methylisocyanate (MITC) are related to each other by virtue of the metabolism of metam sodium and dazomet to MITC. All three metabolize to CS_2.

Mode of Action

No mode of action data were submitted for this chemical.

Classification and Quantification of Carcinogenic Potential

In accordance with the *EPA's Final Guidelines for Carcinogen Risk Assessment* (March, 2005), the CARC classified Metam Sodium as **"Likely to be Carcinogenic to Humans"**. This was based on a treatment-related increase in malignant angiosarcomas in both male and female mice, which exceeded both the range and means of historical controls in both sexes, and had a high incidence in males (up to 52%). No treatment-related tumors were seen in rats. There is no mutagenic concern for metam sodium. No mode of action data were submitted for this chemical.

In 1995, the CPRC recommended that for the purpose of risk characterization, a low dose extrapolation model be applied to the animal data for the quantification of human risk (Q_1*), based on the total incidence of angiosarcomas in male mice, at all sites combined. Based on the current "Likely" classification, the quantification of risk is still required.

I. INTRODUCTION

On February 25, 2009 the Health Effects Division's Cancer Assessment Review Committee (CARC) met to re-evaluate the carcinogenic potential of metam sodium. This was the second carcinogenicity evaluation of metam sodium. The first meeting was conducted by the Carcinogenicity Peer Review Committee (CPRC) on March 1, 1995.

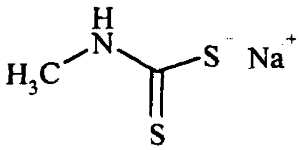
At the 1995 meeting, the CPRC concluded that metam sodium should be classified as a *Group B2 - probable human carcinogen*, based on statistically significant increases in malignant angiosarcomas in both sexes of the CD-1 mouse, supported by a similar tumor type (malignant hemangiosarcomas) in male Wistar rats (HED Document No. 011541). The CPRC recommended that for the purpose of risk characterization, a low dose extrapolation model be applied to the animal data for the quantification of human risk (Q_1*), based on the total incidence of angiosarcomas in male mice, at all sites combined. In March 1995, the HED Carcinogenicity Peer Review Committee estimated a unit risk, Q1* (mg/kg/day), of 1.98×10^{-1} in human equivalents, for metam sodium based upon angiosarcoma rates in male mice (Memo, B. Fisher, 3/10/95, TXR No. 0012954).

Since that time the registrant has submitted a Pathology Working Group (PWG) review of hemangiomatous lesions in the male Wistar rats (MRID 47067501) from the two year chronic toxicity/carcinogenicity study of metam sodium (MRID 43275802). They requested that the CARC re-evaluate the cancer classification of metam sodium based the PWG review and according to the descriptors in the 2005 Guidelines for Carcinogen Risk Assessment.

II. BACKGROUND INFORMATION (From 1995 CPRC report)

Metam Sodium (sodium-N-methyldithiocarbamate), also known as Vapam, Metham Sodium, and SMDC is a fumigant-type pesticide used as a non-selective pre-plant fumigant for control of weeds, nematodes, fungi, bacteria, and insects. There are approximately 35 different products containing metam sodium in concentrations ranging from 18-42% active ingredient. Use patterns for these various formulations include agricultural pre-plant soil fumigation, wood preservative, slimicide, tree root killer, and aquatic weed control. Approximately 10 million pounds of active ingredient were used in 1990, with 40-45% for agricultural purposes. For control of weeds, soilborne diseases, and nematodes infesting field and vegetable crops, the pesticide is applied at least 14 to 21 days prior to planting. As a slimicide, metam sodium is sprayed inside sewer mains and drain pipes; wood preservative uses involve injection of standing utility poles to control wood-destroying insects and to arrest wood rot.

Chemical common name:	Metam Sodium
Type of pesticide:	fumigant
PC Code:	039003
CAS Number:	137-42-8
Chemical name:	sodium- N- methyldithiocarbamate
Structure:	



III. EVALUATION OF CARCINOGENICITY STUDIES

1. Two Year Drinking Water Carcinogenicity Study in Mice

Reference: Homer, S.A. (1994); Metam Sodium: Two Year Drinking study in Mice. Study # PM0841. Study Conducted by Zeneca Central Toxicology Laboratory, Cheshire, UK. MRID # 43233501

A. Experimental Design

In a two year carcinogenicity study in mice, Metam Sodium technical (43.15% active ingredient) was administered in the drinking water to groups of 55 male and 55 female CS7BL/1OJfCD-l/ Alpk mice for 104 weeks at nominal dose levels of 0 and 0.019 mg/ml (1.6 mg/kg/day in males, 2.3 mg/kg/day in females) 0.074 mg/ml (6.5 mg/kg/day in males, 8.7 mg/kg/day in females) and 0.23 mg/ml (27.7 mg/kg/day in males, 29.9 mg/kg/day in females).

B. Discussion of Tumor Data

Carcinogenic potential was evidenced in this study by an increase in the incidence of angiosarcoma of the liver, spleen, subcutaneous tissue, and bone marrow of the femur and spine. **The total number of mice with angiosarcomas, regardless of site, was considered appropriate as a representation of this neoplastic lesion. Regardless of the organ where the tumor originates, all of the angiosarcomas arise from the endothelial cells lining the blood vessels and, therefore, the focus was on the combined tumor incidence. [Note: The 1995 CPRC report presented tables of the angiosarcomas at multiple sites as well as at all sites combined.]** Tumorigenic evidence observed in this study is shown in Tables 1 and 2 (Qualitative Risk Assessment Memo, L. Brunsman, February 1, 1995; TXR No. 0012763).

Table 1. Metam Sodium **Male** Mouse Angioma and Angiosarcoma Tumor Rates [+] and Exact Trend Test and Fisher's Exact Test Results (p- values)

Organs	Dose (mg/kg/day)			
	0	1.6	6.5	27.7
Angiomas[&] (%) p	2[a]/53 (4) 0.378	1/53 (2) 0.500[n]	0/55 (0) 0.239[n]	1/53 (2) 0.500
Angiosarcomas[#] (%) p	7/52 (13) 0.000**	12/52 (23) 0.155	12/55 (22) 0.191	27[b]/52 (52) 0.000**
Combined (%) p	8[c]/52 (15) 0.000**	13/52 (25) 0.164	12/55 (22) 0.273	28/52 (54) 0.000**

[+] Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53.

[n] Negative change from control.

[a] First angioma observed at week 100, dose 0 mg/kg/day.

[b] First angiosarcoma observed at week 68, dose 27.7 mg/kg/day.

[C] One animal in the 0 mg/kg/day dos group had both an angioma and an angiosarcoma.

[&] Angioma sites include: aorta (adjacent tissue), lymph node (mesenteric), and subcutaneous tissue.

[#] Angiosarcoma sites include: abdominal cavity, aorta (adjacent tissue), bone (femur), bone marrow (femur), bone marrow (spine), heart, limb, liver, lung, lymph node (mesenteric), mediastinum, mesentery, spinal cord, spleen, sternum, subcutaneous tissue, and thoracic cavity.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If * , then $p < 0.05$. If ** , then $p < 0.01$.

As shown in Table 1, the statistical significance in tumor incidence for male mice is derived from the angiosarcoma incidence and not from the angioma incidence, which was not statistically different among treated and control male mice. It is noted that a statistically significant positive trend was observed for the incidence of angiosarcoma at all sites combined and for angioma/angiosarcoma combined, as well as a statistically significant pair-wise comparison in the incidence of angiosarcoma and angioma/angiosarcoma combined for male mice at the high dose. The incidence of angiosarcoma in male mice exceeded both the mean and range for the historical controls (Table 3).

Table 2. Metam Sodium **Female** Mouse Angioma and Angiosarcoma Tumor Rates [+] and Exact Trend Test and Fisher's Exact Test Results (p- values)

Organs	Dose (mg/kg/day)			
	0	2.3	8.7	29.9
Angiomas[&] (%) p	1/55 (2) 0.156	0/55 (0) 0.500	2[a]/47 (4) 0.441	2/52 (2) 0.479
Angiosarcomas[#] (%) p	4/54 (7) 0.008**	2/55 (4) 0.331	6[b]/47 (13) 0.286	10/52 (19) 0.065
Combined (%) p	5/54 (9) 0.009**	2/55 (4) 0.211[n]	8/47 (17) 0.194	11[c]/52 (21) 0.075

[+] Number of tumor bearing animals/Number of animals examined, excluding those that died before week 48.

[n] Negative change from control.

[a] First angioma observed at week 87, dose 8.7 mg/kg/day. First angiosarcoma observed at week 48, dose 8.7 mg/kg/day.

[C] One animal in the 29.9 mg/kg/day dose group had both an angioma and an angiosarcoma.

[&] Angioma sites include mammary gland, subcutaneous tissue, and uterus.

[#] Angiosarcoma sites include: bone marrow (femur), bone marrow (spine), ear/ Zymbal's gland, ileum, limb, liver, mediastinum, ovary, salivary gland, spinal cord, spleen, sternum, subcutaneous tissue, and uterus.

Note: Significance of trend denoted at control. Significance of pair-wise comparison with control denoted at dose level.
If *, then p < 0.05. If**, then p < 0.01.

In female mice, there was a significant increasing trend for angiosarcomas at all sites combined (p<0.01). For female combined angiomas and angiosarcomas, there was a significant increasing trend at p<0.01, driven by the angiosarcomas (Table 2), which exceeded both the mean and range of the historical control for female mice (Table 3).

Historical Control Data for Angiosarcomas

Table 3. Historical Controls in Zeneca Mouse Studies
Incidence of Angiosarcoma (including haemangiosarcoma) – all sites

Study No.	Start Date	Sex	
		Male	Female
PM0591	03/84	9/100	9/100
PM0621	02/85	15/100	0/100
PM0628	03/85	9/100	4/100
PM0637	04/85	7/100	5/100
PM0680	11/85	8/100 (7%)	6/100 (7%)
PM0714	03/88	4/60 (5%)	4/60
PM0749	03/89	3/60 (18%)	0/60 (5%)
PM0794	04/90	11/60 (13%)	3/60 (7%)
PM0841	02/91	7/55	4/55

Range Males = 5-18%; Mean = 10%
Range Females = 0-9%; Mean = 4%

C. Non-neoplastic lesions and other findings (From 1995 CPRC report)

Non-neoplastic pathology of the urinary bladder and liver was also observed in this study at the 27.7 mg/kg/day dose level.

When all mice were considered together, the liver and urinary bladder were found to be the main sites of non-neoplastic pathology. At the high dose level (27.7 mg/kg/day in males, 29.9 mg/kg/day in females), increased incidence of epithelial hyperplasia, mononuclear cell infiltration, eosinophilic/hyaline cytoplasmic inclusions, submucosal connective tissue, and submucosal hyalinization were observed in both sexes in the urinary bladder. In the liver, increased incidence of hepatocyte fat vacuolation was observed at the high dose level in both male and female mice.

D. Adequacy of the Dosing for Assessment of Carcinogenicity (From 1995 CPRC report)

At 27.7 mg/kg/day in males and 29.9 mg/kg/day in females, body weight gain in male mice was decreased by 14% vs. control for weeks 1-13 of the study, and by 20% for weeks 1-104 of the study. Liver weight in male mice was increased by 35% over control at this dose level and was accompanied by an increase in fat vacuolation. The incidence of non-neoplastic pathology of the urinary bladder was also increased at 27.7 mg/kg/day in male mice. In female mice, non-neoplastic pathology of the urinary bladder was increased at the 29.9 mg/kg/day dose level. There were no statistically significant effects of treatment on survival in male or female mice. Based on these effects, the high dose level of 27.7 mg/kg/day in males, 29.9 mg/kg/day in females, is considered an adequate dose for assessment of carcinogenic potential in male and female mice.

The 2009 CARC concurred with the previous decision.

2. Two Year Drinking Water Carcinogenicity Study in Rats

Reference: Rattray, N.J. (1994): Metam Sodium: Two Year Drinking Study in Rats. Study # PR0838. Conducted by Zeneca Central Toxicology Laboratory, Cheshire,UK. MRID # 43275802.

A. Experimental Design

Metam Sodium technical (43.14% active ingredient) was administered in drinking water to groups of 64 male and female Hsd/Ola: Wistar Tox rats for either 52 weeks or 104 weeks at dose levels of 0 mg/ml, 0.019 mg/ml (1.3 mg/kg/day in males, 2.3 mg/kg/day in females), 0.056 mg/ml (3.9 mg/kg/day in males, 6.2 mg/kg/day in females), and 0.19 mg/ml (12.0 mg/kg/day in males, 16.2 mg/kg/day in females).

B. Discussion of Tumor Data (From 1995 CPRC report)

Evaluation of tumor data by the California Environmental Protection Agency, Department of Pesticide Regulation indicated a possible tumorigenic effect of metam sodium at the 0.056 mg/ml dose (3.9 mg/kg/day in males, 6.2 mg/kg/day in females). According to their review, the incidence of hemangiosarcoma (8/64) was increased at this dose, in relation to the control incidence (0/64) and the high dose incidence (3/64). The hypothesis that this could be a positive response was based upon the positive findings in mice as well as the reasoning that the increased incidence of this tumor at 0.056 mg/ml (3.9 mg/kg/day in males, 6.2 mg/kg/day in females) could be based upon the decreased body weight observed at the high dose in relation to other doses. Lower body weight has often been shown to be associated with lower tumor incidence in rats.

Evaluation of the liver and pituitary tumor data by the Science Analysis Branch (SAB), Health Effects Division (HED) showed a non-significant trend ($p = 0.119$) for pituitary adenoma in male rats, as well as non-significant pair-wise comparisons between treated and control male rats ($p= 0.323$, 0.234, and 0.129 for the low, mid, and high dose groups, respectively).

For liver adenoma, a non-significant trend was found ($p = 0.246$) as well as a non-significant pair-wise comparison of adenoma incidence among treated male rats ($p = 0.651$, 0.452, and 0.36 for the low, mid and high dose groups, respectively). For liver adenocarcinoma and adenoma/adenocarcinoma combined, similar non-significant trends and comparisons were observed.

A summary of male rat hemangiomatous tumors is shown in Table 4, as analyzed by SAB, HED. There were no statistically significant trends in tumor rates of male rats. However, there was a significant pair-wise comparison in the incidence of hemangiosarcoma in male rats at the 1.3 and 3.9 mg/kg/day dose levels in comparison to control.

Table 4. Metam Sodium **Male** Rat Blood Tumor Rates [+] and Peto's Prevelance Test Results (p-values)

Organs	Dose (mg/kg/day)			
	0	1.3	3.9	12
Hemangiomas (%) p	9[a]/50 (18) 0.469[n]	3/50 (6) 0.950[n]	4[a]/51 (8) 0.899[n]	8/51 (16) 0.688[n]
Hemangiosarcomas (%) p	0/47 (0) 0.414	3/49 (6) 0.017*	8[b]/50 (16) 0.004**	3/51 (6) 0.073
Combined (%) p	9/50 (18) 0.375	6/50 (12) 0.713[n]	11[c]/51 (22) 0.389	11/51 (22) 0.438

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

[a]First hemangioma observed at week 56, dose 0 mg/kg/day.

[b]First hemangiosarcoma observed at week 66, dose 3.9 mg/kg/day.

[C]One animal in the 3.9 mg/kg/day dose group had both a hemangioma and a hemangiosarcoma.

[n]Negative trend or negative change from control.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If, then $p < 0.05$. If ** then $p < 0.01$.

The sites of hemangioma in the present rat study included the cervical lymph node, mesenteric lymph node, thymic lymph node, and subcutaneous tissue. Sites for hemangiosarcoma included the mesenteric lymph node, subcutaneous tissue, tail, liver, lung, and uterus. However, the preponderance of tumors were observed only in male rats.

The question of whether these tumors were observed in separate rats was addressed in the review of the rat study by the California Department of Environmental Protection (Earl Meierhenry, personal communication). This review showed that of the benign hemangiomas found, one rat in the low dose group was found to have this tumor type at 2 sites (mesenteric and thymic lymph nodes). Of the malignant hemangiosarcomas found, 2 rats in the low dose group were found to have this tumor type at 2 and 3 sites (liver and lung; liver, lung, and mesenteric lymph node, respectively).

The hypothesis that increased incidence of hemangiosarcoma observed at the mid dose level (3.9 mg/kg/day in males, 6.2 mg/kg/day in females) vs the high dose level (12.0 mg/kg/day in males, 16.2 mg/kg/day in females) may be based upon a decreased body weight in rats at the high dose is debatable. The rats in this study were not fed a calorie-restricted diet, nor was the amount of dietary intake strictly controlled. Although a statistically decreasing trend in mortality was observed for male rats, food intake, weight gain, and food efficiency were decreased at the 0.19 mg/ml dose (12.0 mg/kg/day in males, 16.2 mg/kg/day in females) in both sexes of rat. In addition, a review of the time to tumor formation for the rats observed with hemangiosarcoma at all dose levels shows that the tumors were observed at approximately the same time (from weeks 93-105), with only one rat at the mid dose observed with this tumor type at an earlier time point (week 66). It has been observed that in calorie-restricted animals, not only can tumor incidence be decreased, but the time to tumor can be delayed. It cannot be proved from the data in this study that such an effect occurred at the high dose.

PWG Reread:

Subsequent to the 1995 CPRC, the registrant submitted a Pathology Working Group (PWG) review of hemangiomatous lesions in the male Wistar rats (MRID 47067501) from the two year chronic toxicity/carcinogenicity study of metam sodium (MRID 43275802). They requested that the CARC re-evaluate the cancer classification of metam sodium based on this review. The PWG review concluded unanimously that the incidence of benign and malignant hemangiomatous tumors in this rat study were not increased by the administration of metam sodium. See Tables 5 and 6.

This PWG was reviewed by HED's pathology consultant, Dr John Pletcher and the conclusions regarding the hemagiomatous tumors in the rat were found to be valid and useful in the weight of evidence evaluation of metam sodium (TXR No. 0055109).

Table 5. Mesenteric Lymph Node Tumors by Group in Wistar Rats

Mesenteric Lymph Nodes (m.l.n)				
		MALES		
Group	Control	Low Dose	Mid Dose	High Dose
Number of rats	64	64	64	64
Number of m.l.n examined	64	64	64	64
Haemangioma	13	6	8	12
Haemangio-sarcoma	0	1	0	0
Angiomatous hyperplasia	4	3	5	3
Lymphangioma	0	2	0	0
All other sites				
Haemangioma	**0**	**0**	**1**	**1**
Haemangio-sarcoma	**0**	**2**	**1**	**0**
Sarcoma	**0**	**0**	**1**	**0**
		FEMALES		
Group	Control	Low Dose	Mid Dose	High Dose
Number of rats	64	64	64	64
Number of m.l.n examined	64	64	64	64
Haemangioma	3	5	7	0
Haemangio-sarcoma	0	0	0	0
Angiomatous hyperplasia	2	1	1	1
Lymphangioma	2	4	1	0
		All other sites		
Haemangioma	**0**	**0**	**0**	**0**
Haemangio-sarcoma	**1**	**0**	**1**	**0**

Table 6. Total Angiomatous Tumors in Wistar Rats

Total angiomatous tumors				
		MALES		
Group	Control	Low Dose	Mid Dose	High Dose
Number of rats	64	64	64	64
Benign tumors only	13	8	9	13
Malignant tumors	0	3	2	0
		FEMALES		
Group	Control	Low Dose	Mid Dose	High Dose
Number of rats	64	64	64	64
Benign tumors only	5	9	8	0
Malignant tumors	1	0	1	0

Benign tumors: haemangioma and lymphangioma
Malignant tumors: haemangiosarcoma

C. Non-Neoplastic Lesions (From 1995 CPRC Report)

At the high dose level, the following were observed: decreased body weight gain for weeks 1-13 (12% males, 16% females) and for weeks 1-105 (18% in males, 20% in females). Decreased food consumption, food efficiency, and water consumption was noted in male and female rats. Increased incidence of liver masses (8/64 vs 4/64 in control) and fat vacuolation (11/32 vs 8/28 in control) was present in male rats. Also an increased incidence of voluntary muscle wasting (9/64 vs 1/64 in control) was noted in male rats. In addition, an increased incidence of microscopic abnormalities of the nasal cavity, voluntary muscle, and sciatic nerve, as well as decreased incidence of mineralization of the aorta in male and/or female rats were noted.

D. Adequacy of Dosing for Assessment of Carcinogenicity (From 1995 CPRC Report)

Further details of these changes can be seen in the data evaluation record (DER) for this study, as the changes are too numerous to reproduce here.

The high dose of 0.19 mg/ml (12.0 mg/kg/day in males and 16.2 mg/kg/day in females) was considered adequate for testing of the carcinogenic potential of metam sodium in rats, based on the decreases in body weight gain, food efficiency, and macroscopic and microscopic pathology observed in both sexes in this study.

The 2009 CARC concurred with the 1995 decision.

IV. TOXICOLOGY

1. Metabolism (From 1995 CPRC Report)

Reference: Hawkins, D.R., Elsom, L.F., and Girkin, G. (1987): The Biokinetics and Metabolism of 14C-Metam Sodium in the Rat. Study conducted by Huntington Research Centre, Cambridgeshire, UK and submitted under MRID No. 406410-00.

Single oral doses of 10 mg/kg and 100 mg/kg ^{14}C-Metam sodium (purity > 99%) were administered to groups of male and female Sprague-Dawley rats (# rats per group not specified). Urine and feces were collected up to 168 hours post-dose, while expired air was collected up to 72 hours post-dose. The time course of radioactivity in plasma was also investigated at the 10 and 100 mg/kg dose levels in five rats/sex/dose.

At the 10 mg/kg dose, urine was the major route of excretion, representing between 52-58% of the administered dose. Excretion through expired air represented between 32-38% of the administered dose, while between 3-4% was excreted through feces. At the 100 mg/kg dose, urinary excretion was decreased to between 37-42% of the administered dose, while excretion through expired air increased to between 47-53% of the administered dose. Fecal excretion remained low (between 1.5-1.8% of the administered dose).

At the low dose, the majority of collected radioactivity in expired air represented CO_2 (18-19% of administered dose) or COS and/or CS_2 (14-18% of the administered dose). A minor amount of MITC was observed (0.45-1.26% of the administered dose). At the high dose, the majority of collected radioactivity in expired air represented MITC (24-24.5% of the administered dose) and COS and/or CS_2 (18-21% of the administered dose), with only minor amounts of CO2 (5.5-7.2% of the administered dose).

The time course of excretion was similar at the 10 and 100 mg/kg dose, with the shift being primarily in the percentages excreted through urine and expired air. A shift in biotransformation is indicated at the 100 mg/kg dose.

Tissue distribution at 168 hours post-dose showed the highest amounts of radioactivity in the thyroid (1.28-3.09 µg/g at 10 mg/kg; 6.24-7.55 µg/g at 100 mg/kg). Relative to other tissues, high concentrations of residual radioactivity were also observed in the liver, lung, and kidney. In general, tissue levels ware higher in female rats than male rats at 168 hours.

Results of plasma time course measurements showed a T_{max} of 1.0 hours at the 10 mg/kg dose in both sexes, and a T_{max} of 0.25-1.0 hours at the 100 mg/kg dose. Half-life of elimination was unaffected by the increase in dose (60.8-74.1 hours at the 10 mg/kg dose [males and females]); 61.7-64.2 hours at 100 mg/kg [males and females]), and AUC was proportional to dose, indicating first-order kinetics at both dose levels.

The urinary and tissue profile of metam sodium metabolites was similar to that observed following dazomet administration; that is, the N-acetylcysteine conjugate of methyl isothiocyanate (MITC) was identified in urine as a major component (16.1-23.3% of the administered dose) at both dose levels, as was the glycine conjugate of MITC (5.1-8.2% of the administered dose at both dose levels). In the liver and kidney, the N-acetylcysteine conjugate of MITC was also identified as the major metabolite, as was the case for dazomet.

2. Mutagenicity (From 1995 CPRC Report)

i.) Cifone, M.A. (1987): Mutagenicity Test on Metam Sodium in the Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay. Study # HLA 9736-0-447. Study performed by Hazelton Laboratories America, Inc. and submitted under MRID# 403056-01.

In this study, freshly isolated hepatocytes from male Fischer 344 rat liver were incubated with metam sodium at concentrations of 0.5, 1.0, 2.5, 5.0, 10.0, 50.0, 100.0, and 250.0 nl/ml. Incubations were at 37° C for 18-20 hours in the presence of tritiated thymidine. The 250 nl/ml dose was selected based on the results of preliminary testing showing a relative survival range of 17% at 100 nl/ml to 55.3% at 50 nl/ml. Results of the main study showed that metam sodium caused no significant changes in nuclear labeling of primary rat hepatocytes at the concentrations tested.

Classification: acceptable (HED document # 006570).

ii) Hoorn, A.J. (1987): Mutagenicity Test on Metam Sodium in the Rec Assay with Bacillus subtilis. Study # HBC E-9642-0-404. Study performed by Hazelton Biotechnologies Veenedal Lab, Netherlands, and submitted under MRID # 403056-02.

In this study, Bacillus subtilis strains H17 and M45 were incubated in the absence and presence of metabolic activation (rat liver S-9) with metam sodium at doses of 0.1, 1.0, 5.0, 10.0, 25.0, 50.0, 100.0, and 150.0µl/plate. Metam sodium failed to induce differential toxicity in Bacillus subtilis strains H17 and M45 at the concentrations tested.

Classification: acceptable (HED document # 007027).

iii) Engelhardt, G. (1987): Report on the Study of Metam Sodium in the Ames Test. Study # BASF 87/0208. Study performed by BASF Aktiengeselleschaft Dept. of Toxicology, FRG and submitted under MRID # 403056-03.

In this study, metam sodium was non-mutagenic to Ames Salmonella typhimurium strains TA92, TA98, TA100, TA1535, TA1537, and TA1538 in the absence or presence of metabolic activation (rat liver S-9). Concentrations tested were: 20, 100, 500, 1000, 1500, 2000, and 2500 µg/plate in the standard plate test, and 4, 20, 100, 200, 300, 400, 500, 1000, and 2500 1µg/plate, in the pre- incubation test.

Classification: acceptable (HED document # 006570).

iv.) Gelbke, H.P. (1987): In Vitro Cytogenetic Investigation in Human Lymphocytes with Metam Sodium. Study # BASF 87/0116. Study Performed by BASF Aktiengeselleschaft Dept. of Toxicology, FRG and submitted under MRID # 403056-04.

In this study, 48-hour cultures of human lymphocytes were exposed to 1, 5, 10, and 20 µg/ml metam sodium in the absence of metabolic activation and to 10, 20, and 40 µg/ml metam sodium in the presence of rat liver S-9. Incubations were for 24 hours at 37° C. In the absence and presence of metabolic activation, metam sodium demonstrated a dose-dependent and statistically significant increase in the number of chromosomally damaged cells. There was no significant increase in the numerical chromosome aberrations in treated vs solvent controls. When these data were revisited, it was concluded that the significant increase in structural chromosome aberrations under nonactivated conditions was accompanied by severe cytotoxicity as noted by the study authors and only 100 metaphases were available for analysis. Thus, the nonactivated findings should be listed as positive but qualified with respect to cytotoxicity. In the presence of S9 activation, significant increases in structural chromosome aberrations were seen at 20 and 40 ug/mL; the predominant type of aberration was chromatid breaks, which are frequently associated with cytotoxicity.

Classification: acceptable. (HED document # 006570).

v.) Gelbke, H.P. and Engelhardt, G. (1987): Cytogenetic Study in Vivo of Metam Sodium in Chinese Hamsters, Bone Marrow Chromosome Analysis. Study # BASF 87/0238. Study performed by BASF Aktiengeselleschaft Dept. of Toxicology, FRG and submitted under MRID # 403056-05.

Metam sodium was tested for clastogenicity in Chinese hamsters after single oral doses of 150, 300, and 600 mg/kg. Five animals per sex were sacrificed at 6, 24, and 48 hours post-dose for examination of bone marrow cells. At the dose levels tested, metam sodium was not positive in Chinese hamster bone marrow.

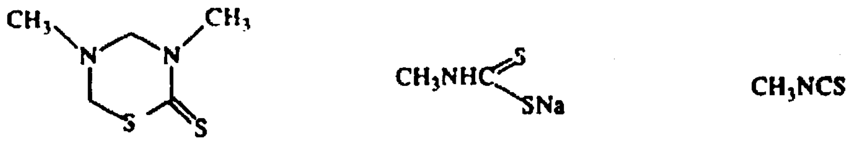
Classification: acceptable (HED document # 007027).

Conclusion: Metam sodium was not mutagenic and did not induce DNA damage in bacteria (*S. typhimurium* or *B. subtilis*, respectively). Similarly, it did not induce unscheduled DNA synthesis in primary rat hepatocytes or chromosome aberrations in the bone marrow of Chinese hamsters. The relevance, if any, of the positive *in vitro* chromosome aberration assay in the presence of S9 activation is not clear. Based on the evaluation of other methyldithiocarbamates, it was concluded that mutagenicity data are not predictive of carcinogenicity for this chemical class because positive results in bacterial tests and *in vitro* mammalian cell chromosomes aberration assays have been seen with noncarcinogenic methyldithiocarbamates (See TXR No. 00511541). Based on these considerations, there is no mutagenic concern for metam sodium.

In the original CPRC report (March 1, 1995), there was a recommendation for a dominant lethal assay based on the structural aberrations seen in human lymphocytes with metam sodium, both in the presence and absence of metabolic activation. Since re-evaluation of that data determined that there was severe cytotoxicity under the nonactivated conditions, and because there were no other findings raising a mutagenic concern, the CARC concluded at the present meeting that a dominant lethal assay was no longer required.

3. Structure-Activity Relationship

Metam sodium, dazomet and methyisocyanate (MITC) are related to each other in that metam sodium and dazomet are bother precursors to MITC. All three metabolize to CS_2. Structures of these chemicals are as follows:



Dazomet Metam Sodium Methyl isothiocyanate (MITC)

MITC

Drinking water carcinogenicity studies have been performed for this chemical in both rats and mice, and these data have been submitted to HED for review (Accession #'s 257766 and 257759-257763). Although both studies were core graded as supplementary data, administration of MITC in drinking water did not appear to result in increased incidence of tumors in either rats or mice. However, the dose levels tested were not considered adequate for evaluation of the carcinogenic potential of MITC. The results of these studies have also been published in *Nippon Noyaku Gakki Shi* 15(2): 297-304 (1990), which concluded that no carcinogenic activity was observed for MITC in drinking water studies with rats and mice. Metam sodium was originally classified as Group B-Probable Human Carcinogen by the Agency. Metabolically, metam sodium is converted to MITC and a significant amount of carbon disulfide (see below) is also formed. On 2/22/2000 MITC was classified as Group B - Probable human carcinogen based on data of the parent compound (metam sodium).

Dazomet

Dazomet has been subject to peer review through the Health Effects Division Carcinogenicity Peer Review Committee. This chemical was classified as Group D - not classifiable as to human carcinogenicity. This decision was based upon both rat and mouse studies submitted to and reviewed by Toxicology Branch II. In the submitted mouse study (MRID # 41865101), female mice were found to have a significant dose-related trend in hepatocellular adenoma and combined adenoma/carcinoma. No significant pair-wise comparisons with control were evident, and the prevalence of this tumor type in the B6C3F1 mouse made it difficult to assign the tumors as a treatment related effect.

In the submitted rat study (MRID # 41865001), there appeared to be no treatment related effect on the incidence of tumors in male and female rats.

Carbon disulfide

Carbon disulfide (CS_2) is one of the primary metabolic products of metam sodium after administration of a low (10 mg/kg) or high (100 mg/kg) oral dose (see metabolism study section of this memo). In the July 1994 update on the Toxicological Profile for carbon disulfide (U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry), it was stated that there is no definitive evidence for an increased cancer potential from carbon disulfide in humans. Although an increased odds ratio for lymphocytic leukemia in rubber workers exposed to different kinds of solvents including CS_2 was reported, the large number of solvents used and design of the study preclude definitive association of CS_2 exposure with tumor development. In experimental animals, exposure of the A/J strain of mouse (females) to 300 ppm CS_2 for 6 hours/day, 5 days/week for 6 months resulted in a slight but statistically significant increase in the number of pulmonary adenomas per mouse and the number of tumors per tumor-bearing mouse lung (Van Stee *et al.*, J. Toxicol. Env. Health, 17: 311-322, 1986). There are no chronic toxicity or carcinogenicity animal studies in the Agency's toxicology database for carbon disulfide.

4. Subchronic and Chronic Toxicity (from the 1995 CPRC Report)

a) Subchronic Toxicity

Rats (MRID #42117302)

In a 90-day oral toxicity study (MRID 42117302), Alpk:APfSD (Wistar derived) SPF rats (12/sex/group) were given metam sodium (45.13%, Batch No. BAS 005/00N) administered in drinking water at nominal dose levels of 0, 0.018, 0.089, and 0.443 mg/ ml [1.7, 8.1, and 26.9 mg/kg/day (0.95, 4.54, and 15.06 mg/kg/day MITC equivalent) in males; 2.5, 9.3, and 30.6 mg/kg/day (1.4, 5.21, and 17.34 mg/kg/day MITC equivalent) in females]. Drinking water was prepared daily and water from the previous day was discarded.

A female at the high dose level was killed for humane reasons on day 5. Necropsy revealed cystitis, granulocytic hyperplasia (sternal marrow), unilateral hydronephrosis, pyelonephrosis, lymphadenitis, gastric hemorrhagic foci, hyperplasia of the ureter, and inverted thymus.

Mean body weights were significantly decreased (p<0.01,-22%) during weeks 1-14 in high-dose males and females, and -4% during weeks 5 and 7-14 in mid-dose females, when compared to controls. High-dose animals demonstrated a dramatic decrease in body weight gain of 45% and 63% during weeks 1-7, and 37 and 49% during weeks 1-4 in males and females, respectively when compared to controls.

Significant decreases in mean food consumption were noted throughout the study in high- dose males (p<0.0 1, 20-36%) and females (p<0.0 1, 20-50%), when compared to controls. Water consumption was reduced by 50-70% in both sexes at the high dose group and by 30% in females at the mid dose group throughout the study. There were no changes in water consumption in males at the mid dose level or either sex at the low dose level. Decreased water consumption was likely due to poor palatibility.

Qualitative urinalyses demonstrated a slight increase of blood in the urine in some males at all doses. However, the magnitude of this change was not the same for all males, and not all males were affected. There were an increase number of animals (both sexes) exhibiting renal epithelial cells in the urinary sediment at mid-and high-dose, and slightly increased numbers of females (all doses) exhibiting red and white blood cells in urinary sediment.

The kidney appeared to be a target organ, with findings of renal tubular dilatation and basophilia, along with increases in blood, protein, and red blood cells, and renal epithelial cells in urine in treated animals. Other incidences above control values were noted at high dose as hyperplasia in cervical lymph node cells.

Significant decreases ($p \leq 0.05$; 9%) in the platelet counts of high-dose males were noted compared to controls, however, none were found in the high-dose females. Significant decreases in red cell count (all dose level for female and mid and high dose level for male) and hematocrit (all dose level for male and female) was also observed.

Significant decreases in mean absolute organ weight occurred in both male (36%) and female (43%) high dose animals when compared to controls, for all organs weighed, except kidneys (female) and testes. The decreases in absolute organ weight were primarily due to decreased body weight gain, since the relative organ weight remained stable. Furthermore, with the exception of a slight increase in kidney (high-dose females) and liver weights (mid-dose females), there was no significant difference in organ weight adjusted for body weight for any group.

Nasal cavity alterations were noted in high dose animals, as increased incidences of vascuolated Bowman's gland/ducts (olfactory epithelium), vacuolated olfactory epithelium, disorganization of nasal epithelium (both sexes), and increased incidences of necrosis of nasal cavity (females).

The LOAEL is 8.1 mg/kg/day (4.54 mg/kg/day MITC equi.) in males based on hematological changes (kidney) and 9.3 mg/kg/day (5.21 mg/kg/day MITC equi.) in females based on decreased absolute body weight. Nasal cavity pathology were likely due to MITC.

The NOAEL is 1.7 mg/kg/day (0.95 mg/kg/day MITC equi.) in males and 2.5 mg/kg/day in females.

This 90-day oral toxicity study in the rat is **unacceptable-guideline** and does **not** satisfy the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3150; OECD 409) in rodent species. A deficiency in the study existed in the collection of food and water consumption data which was not performed for individual animals as per the guidelines. Kidney as a target organ was not examined histologically in low and mid-dose groups as per guidelines; this examination might have clarified possible treatment-related effects. The kidney was also affected in subchronic oral toxicity study in mice at dose levels of 0.35 and 0.62 mg/ml. Analyses of the drinking water were not performed during the study due to "analytical problems." Analyses were performed 6-12 months after completion of the study. Stability of the test material in the water samples were outside of acceptable limits, for all levels tested, with low and mid-dose values <40% of nominal concentrations.

Rats (MRID # 00162041)

In a 90-day inhalation (MRID no. 00162041), 18 Sprague-Dawley rats/sex/dose group were exposed to aerosolized metam sodium (37% a.i.) in whole-body chambers for 6 hr/day, 5 days/week. The cumulative mean chamber metam sodium concentrations were 0, 6.5, 45 and 160 mg/m^3 (measured values based on the sodium ion level corrected for sodium ion levels measured from the control). Reviewers at the California Department of Pesticide Regulation calculated the doses to be 0, 1.11, 7.71, and 27.43 mg/kg/day. Mean MITC measured concentrations were 0, 0.78, 2.2, and 5.7 $mg/\ m^3$ (0, 0.12, 0.38, 0.98 mg/kg/day) (measured by infrared adsorption).

Clinical signs of salivation, dullness, chromodacryorhea, dehydration, rough coat, and wet coat were noted in males and females of the highest concentration level. There were no treatment related mortalities.

Body weight gain was reduced at the highest concentration level compared to control (- 6% and - 8% for males and females). Food consumption was decreased compared to control in the mid and highest levels (-8% and - 10%).

At the interim measurement, plasma lactate dehydrogenase levels were statistically reduced compared by 50°/o and 62% (p< 0.05) in females in the mid and high dose levels but only the highest dose in males (-18%). At termination, albumin was decreased compared to control (-13% and -22%; p<0.05) and alkaline phosphatase increased (+2- fold; p<0.05) at the mid and high dose levels in females only.

Although the absolute weights were not affected, significant increases in relative lung (+13% males, +21% females) and kidney (+7% males, +14% females) weights were noted in the highest dose group.

Histopathology indicative of irritation was noted in the nasal passages, lung, and stomach. A dose-dependant increase in the incidence of mucigenic hyperplasia of the nasal passage was noted in all treatment groups for females but only reached statistical significance in the mid and high dose group. This finding (ie, incidence of mucigenic hyperplasia) was increased ($p<0.05$) only in the male high dose group. Mucigenic cysts were noted in 2 females of the highest dose group. A dose-dependant increase in lymphocytic rhinitis was noted in all treatment groups although statistical significance was noted only at the mid and high dose males. In the lungs, histiocytosis was noted in 3/27 high dose males and 2/18 high dose females. In the stomach, erosive gastritus was statistically increased in the high dose males and females (9/17 males, 13/18 females). Ulcerative gastritis was noted in 2/18 high dose females. Gross pathological changes in stomach were also noted at the high dose in males and females by in an increased incidence in red/black foci or streaks.

The LOAEL in females is 45 mg/m^3 (7.71 mg/kg/day) of metam sodium (based on Na levels; 2.2 mg/ m^3 10.38 mg/kg/day measured MITC), based on histopathological changes in the nasal passages (ie, mucigenic hyperplasia) and changes in clinical chemistry. The LOAEL in males is 160 mg/ m^3 (27.43 mg/kg/day) of metam sodium (based on Na levels; 5.7 mg/ m^3 10.98 mg/kg/day) based on histopathological changes in the lungs and nasal passages.

The NOAEL for females is 6.5 mg/ m^3 (1.11 mg/kg/day) of metam sodium (based on Na levels; 0.7 mg/ m^3 10.12 mg/kg/day measured MITC). The NOAEL for males is 45 mg/ m^3 (7.71 mg/kg/day) of metam sodium (based on Na levels; 2.2 mg/ m^3 [0.38 mg/kg/day] measured MITC).

This subchronic inhalation toxicity study in the rat is acceptable-guideline and satisfies the guideline requirement for a subchronic inhalation study OPPTS 870.3465; OECD 413 in the rat.

Mouse (MRID# 42117301)

In a 90-day oral toxicity study (MRID 42117301) metam sodium (45.13% w/w, Batch No. BAS/005/00N and CLT Reference No. Y06930/007 and Y06930/008) was administered to C57BL/I0JfAP/Alpk strain mice (30/sex/dose) in drinking water at the dose levels of 0, 0.018, 0.088, 0.35, and 0.62 mg/ml [0, 2.7, 11.7, 52.4, and 78.7 mg/kg/day (0, 1.51, 6.55, 29.34 and 44.07 mg/kg/day MITC equivalent) for males and 0, 3.6, 15.2, 55.4, and 83.8 mg/kg/day (0, 2.02, 8.51, 31.02 and 46.93 mg/kg/day MITC equivalent) for females] for 90 days. Drinking water was prepared daily, except for on occasions at the start of the study where the control and 0.62 mg/ml dosing preparations were used over a three and two-day period.

No treatment-related mortality or clinical signs of toxicity were observed in any of the treated animals during the 90-day study period. Treatment-related statistically significant decreases in mean body weight were observed in both female and male mice at doses of 0.35 and 0.62 mg/ml as early as weeks 2-3 and persisted throughout most of the remainder of the 13-week study period. A reduction of up to 11% and 13% in female and male respectively, at the 0.62 mg/ml dose level and a reduction of up to 8% and 9% in the female and male respectively, at the 0.35 mg/ml dose level was noted. There were statistically significant decreases in total water consumption during weeks 1-13 in the males at the 0.62 mg/ml (-24%) dose level, and in females at dose levels of 0.35 mg/ml (-27%) and 0.62 mg/ml (-44%), as compared to their respective controls.

At termination of the study treatment-related changes in hematological parameters were observed at doses as low as 0.088 mg/ml in females and 0.35 mg/ml in males. At dose levels 0.088, 0.35 and 0.62 mg/ml in females, statistically significant dose-related decreases in hemoglobin (HGB), hematocrit (HCT), and red blood cell count (RBC) were observed. At 0.35 and 0.62 mg/ml, dose-related statistically significant decreases were observed in males for RBC and HGB.

Microscopic examinations were performed on the interim kill animals from the control and highest dose (0.62 mg/ml) groups. At the 0.62 mg/ml dose level, one male had slight centrilobular hypertrophy of the liver, and two females had minimal inflammatory cell infiltration of the liver which was not observed in any of the control animals. Also, one female at high dose level had a cystic gland in the stomach. This observation was not reported for any control animals.

At terminal sacrifice, there were statistically significant increases for males and females in absolute liver weight at doses of 0.35 mg/ml (↑13% and ↑16%, respectively) and 0.62 mg/ml (↑ 17% and ↑ 13%, respectively), and in liver weight adjusted for body weight at doses of 0.088 mg/ml (↑8% and ↑5%, respectively), 0.35 mg/ml (↑22% and ↑21%, respectively) and 0.62 mg/ml (↑21% and ↑19%, respectively, as compared to their respective controls. Also at terminal sacrifice, microscopic findings of the liver consisted of slight periportal hepatocyte vacuolation, slight microvesicular changes in centrilobular hepatocytes, and minimal inflammatory cell infiltration. None of the reported microscopic abnormalities of the liver were considered to be treatment related as the same frequencies of abnormalities were observed in both treated and control animals and no dose-response was seen.

At terminal sacrifice, there were statistically significant increases for males and females in kidney weight adjusted for body weight at doses 0.35 mg/ml (↑10% and ↑9%, respectively) and 0.62 mg/ml (↑9% and ↑10%, respectively, as compared to their respective controls). At termination of the study microscopic findings a polycystic kidney (marked severity) was reported in 1/10 males at a dose of 0.35 mg/ml and 1/10 females at a dose of 0.62 mg/ml.

At termination of the study microscopic findings of the urinary bladder were reported for males and females at doses of 0.088, 0.35, and 0.62 mg/ml. Cystitis was observed in 8/8 females and 10/10 males from the 0.35 mg/ml dose group, and 3/10 females and 8/10 males from the 0.62 mg/ml dose group. Mucosal hyperplasia was observed in 7/8 females and 10/10 males from the 0.35 mg/ml dose group, and 8/10 females and 9/10 males from the 0.62 mg/ml dose group. Eosinophilic granules in the bladder epithelium were reported for 10/10 males and 10/10 females at 0.088 and 0.62 mg/ml, and 7/10 males and 8/8 females at the 0.35 mg/ml dose group. No incidence was reported in the control and 0.018 mg/ml dose groups.

The systemic LOAEL was 0.088 mg/mL [11.7 and 15.2 mg/kg/day (6.55 and 8.51 mg/kg/day MITC equi.) for males and females, respectively] based on urinary bladder lesions (eosinophiic granules, cystitits and mucosal hyperplasia) in both sexes and decrease in hematological parameters (hemoglobin, RBC, hematocrit) in female mice. The systemic NOAEL was 0.018 mg/ml 12.7 and 3.6 mg/kg/day (1.51 and 2.02 mg/kg/day MITC equi.) for males and females, respectively].

This 90-day oral toxicity study in the mouse is unacceptable-guideline and does not satisfy the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3150; OECD 409) in rodent species. Clinical blood .chemistries and ophthamological examinations were not performed during this study (however, clinical chemistry was affected in the chronic mouse study). The significant instability of metam sodium in water after 24 hours, especially at the concentration of 0.018 mg/ml (29.1-31.5% of initial concentration remained after 24 hours), make it not possible to determine the actual amount of test article administered to the animals.

b) Chronic Toxicity

Rats (MRID# 43275802)
Carcinogenicity Study

In a two year combined chronic toxicity/carcinogenicity study (MRID 43275802), metam sodium technical (43.14% a.i., Sample Reference No. BAS/005/005 90-2) was administered in drinking water to groups of 64 male and female rats for either 52 weeks or 104 weeks at dose levels of 0, 0.019, 0.056, and 0.19 mg/mL (0, 1.3, 3.9, and 12.0 mg/kg/day metam sodium). 12 animals were sacrificed at week 52 of the study. The drinking water was prepared daily throughout the study.

There were no significant effects if treatment on mortality in male and female rats during the study period. However, at week 105, mortality in control male rats appeared unacceptably high (less than 25% alive at week 105). The number of male rats found dead was 7, 3, 2, and 1 for the 0, 0.019, 0.056, and 0.19 mg/ml dose levels, respectively. Mortality in female rats at all dose levels was much less at week 105 in relation to male rats. There were historical control data provided with which to make a comparison of mortality in this strain of rats.

Effects on body weight gain were observed at the 0.19 mg/ml dose level in both male and female rats, where weight gain was decreased by 12-18% in males and 16-20% in females vs control over the course of the study period. At the 0.056 mg/ml dose level, body weight gain was unaffected in male rats, and was decreased by approximately 8-9% in female rats over the course of the study period.

In both male and female rats at the 0.19 mg/ml dose level, food consumption was decreased by

10% relative to the control for weeks 1-13 if the study. At weeks 52 and 104, decreases were also observed in both sexes at the 0.0 19 mg/ml dose level, ranging from 4-19% below control values. Efficiency of food utilization was decreased in male rats at the high dose for weeks 1-12 of the study. While this was labeled as statistically significant, this represented a decrease of only 3% from control.

Statistically significant decreases in water consumption were noted in both male and female rats at the 0.056 and 0.19 mg/ml dose levels. Female rats appeared to be affected in a greater manner than male rats at these two dose levels. Mean water consumption for weeks 1-13 of the study was decreased in treated male rats by 4.2%, 9.6%, and 3 7.9% compared to control at the 0.019, 0.056, and 0.19 mg/ml dose levels, respectively. In females, the decreases were 4.8%, 24%, and 54.2% at the 0.0 19, 0.056, and 0.19 mg/ml dose levels.

Reduction (statistical significance) in urine volume was observed in male (34%) and female (33%) rats at week 78 at the 0.19 mg/ml dose level.

Effects on hematology (decreased red blood cells (RBC), hemoglobin (HGB), hematocrit (HCT)) and clinical chemistry (decreased cholesterol and triglycerides) was observed in both sexes. At the 0.19 mg/ml dose level, both male and female rats showed a consistent decrease of 3 to 4% form control in mean HGB and RBC throughout the study. The largest decrease in these parameters occurred at week 105, where HGB was decreased 12% high dose males and 5% in high dose females, with HCT and RBC following a similar pattern. At weeks 79 and 105, both plasma cholesterol and triglycerides were decreased in female and male rats at the 0.19 mg/ml dose level. For cholesterol, the decreases ranged from 4-10% in males, and 17-19% in females. For triglycerides, the decrease ranged from 22-43% in females, and 18-32% in males. These changes in hematology parameters did not always achieved statistical significance, were isolated and inconsistent and therefore considered not to be of biological significance.

At both the interim sacrifice and terminal kill time, organ weight changes were noted in the adrenal glands and kidneys. The effects on organ weight were not consistent between sexes. Adrenal weight in male rats at the 0.19 mg/ml dose level from the interim sacrifice group was decreased by 10% compared to control, while adrenal weight in female rats at the same dose level and time point was increased by 36% from control. At the terminal sacrifice time, no significant changes were observed in adrenal weight. Kidney weight was noted to be decreased significantly in male rats at the 0.19 mg/ml dose level from the interim sacrifice time point (decrease of 12% from control), but no effects were observed in female rats. At the terminal sacrifice time point, the same percentage decrease was observed in male rats at the 0.0 19 mg/ml dose level, but was not considered to be statistically significant.

Increased number of liver masses and increased incidence of fat vacuolation of the liver were observed in male rats at the 0.19 mg/ml dose level, as was increased incidence of wasting of voluntary muscle.

Microscopic abnormalities of the nasal cavity (increased incidence of rhinitis, hypertrophy of

Bowman's ducts/glands, atrophy and adenitis of Steno's gland, and olfactory epithelium hyperplasia and degeneration), heart and aorta (decreased mineralization), liver (spongiosis/ peliosis hepatitis with altered hepatocytes) voluntary muscle (increased severity of degenerative myopathy), and sciatic nerve (increased severity of degeneration) were observed in male and/or female rats at the 0.19 mg/ml dose level.

The changes observed in the adrenal gland, aorta, heart, and liver were confined primarily in the male rats, while the remaining changes were observed in both sexes.

The LOAEL is 0.19 mg/ml [12.0 and 16.2 mg/kg/day (6.72 and 9.07 mg/kg/day MITC eqvi.) for males and females, respectively], based on the changes in body weight gain, food efficiency, hematologic and clinical chemistry alterations, and macro- and microscopic abnormalities observed at this dose in both sexes.

The NOAEL is 0.056 mg/ml 13.9 and 6.2 mg/kg/day (2.18 and 3.47 mg/kg/day MITC eqvi.) for males and females, respectively].

This chronic/carcinogenicity study in the rat is acceptable-guideline and satisfies the guideline requirement for a chronic/ carcinogenicity study OPPTS 870.4300); OECD 453] in rat.

Mouse (MRID# 42233501)

In a two-year carcinogenicity study in mice (MRID 43233501), metam sodium (43.15% w/w active ingredient concentration in liquid form (525.54 g/L, Sample Reference No. BAS/005/00N 90-2) was administered to C57BL/10JfCD-l/Mpk mice (55/sex/dose) in drinking water for 104 weeks at nominal dose levels of 0, 0.019,0.074, and 0.23 mg/ml (1.6, 6.5, and 27.7 mg/kg (0.896, 3.64 and 15.51 mg/kg MITC equivalent) for male mice and 2.3, 8.7, and 29.9 mg/kg(1.29, 4.87 and 16.74 mg/kg MITC equivalent) for female mice. Drinking water was daily in batches of 2.5 or 5 liters.

There were no apparent treatment related effects on mortality in either male or female mice in this study. The decrease in the number of female mice alive between weeks 1 and 27 at the 0.074 mg/ml dose level was due to accidental death of 5 female mice at week 25. The cause of the accident was not stated.

Group mean body weight gain was reduced at the high dose level for both sexes of mice. The decrease was more pronounced in the male mice than the female mice, as shown by the 14% decrease for weeks 1-13 at the 0.23 mg/ml dose level and the 20% decrease for the entire study period. The decrease in females did not exceed 10% of the control.

In male mice, significant food consumption decreases were observed during the first 13 weeks (2, 5, and 7 through 11) of the study at the 0.23 mg/ml dose level. These decreases, while identified as statistically significant, were on the average of 5%. In females, no significant decreases in food consumption were recorded for the first 13 weeks of the study. Total food consumption for both male and female mice for the first 13 weeks of the study was not affected in treated compare to control mice.

Water consumption in male and female mice was decreased during the first week of the study, and was statistically significant at the 0.23 mg/ml dose level for both sexes, and at all dose levels for the male mice. This trend continued in male mice for the first 2 weeks of the study, and then by week 9, was increased at the 0.23 mg/ml dose level. In female mice, water consumption at the 0.23 mg/ml dose level tend to decrease relative to control, but statistical significance was not consistently achieved.

At 0.074 and 0.23 mg/ml dose levels, statistically significant increases in absolute liver weight were observed in both the male and female mice. The increase in liver weight for male mice was 111% and 135% of control at the 0.074 and 0.23 mg/ml dose levels, respectively, while the increase for female mice was 119% and 122% of control at the same dose levels. Kidney weight was decreased by 9% in male mice at the 0.074 and 0.23 mg/ml dose levels and was increased by approximately the same percentage in female mice at these dose levels. There were no other significant organ weight changes reported in the study.

Increases in the incidence of macroscopic pathology were observed in the liver (accentuated lobular pattern, pale appearance) and urinary bladder (wall thickening) at the 0.23 mg/ml dose level. Non-neoplastic pathology in male and female mice was increased at 0.23 mg/ml, and included increases in extramedullary hemopoiesis of the spleen and several alterations in the urinary bladder, including epithelial hyperplasia, eosinophilic/hyaline cytoplasmic inclusions, increased submucosal connective tissue, and submucosal hyalinization.

The LOAEL is 0.074 mg/ml [16.5 mg/kg (3.64 mg/kg MITC equi.) in males, 8.7 mg/kg (4.76 mg/kg MITC equi.) in females], based upon the significant increase in liver weight, and decrease body weight gain, food and water consumption in male and female mice. The NOAEL is 0.019 mg/ml [1.6 mg/kg in males (.89 mg/kg MITC equi.), and 2.3 mg/kg (1.29 mg/kg MITC equi.) in females].

This carcinogenicity study in the mice is **acceptable/guideline** and satisfies the guideline requirement for a carcinogenicity study [OPPTS 870.4200; OECD 451] in mice.

5. Mode of Action Studies

No specific mode of action study is available for metam sodium.

V. COMMITTEE'S ASSESSMENT OF THE WEIGHT-OF-THE-EVIDENCE

The Committee considered the following for a weight-of-evidence determination on the carcinogenic potential of metam sodium:

1. Carcinogenicity

Mouse

- Administration of metam sodium in the drinking water to CD-1 male mice resulted in a significant increasing trend and a significant difference in the pair-wise comparison of the high dose with the control for angiosarcomas all sites combined, both at ($p<0.01$ For combined angiomas and angiosarcomas, there was a significant increasing trend as well as a significant difference in the pair-wise comparison of the high dose group with the controls, both at ($p<0.01$), and both of which were driven by the angiosarcomas. In female mice, there was a significant increasing trend for angiosarcomas at all sites combined ($p<0.01$). For female combined angiomas and angiosarcomas, there was a significant increasing trend at $p<0.01$, driven by the angiosarcomas. **Therefore, the CARC considered the angiosarcomas in male and female mice to be treatment-related.**
- *Adequacy of Dosing*: Dosing in the mouse study was considered to be adequate at the high dose for assessing the carcinogenic potential of metam sodium in both sexes. This was based on decreased body weight gain, increased liver weight, and fat vacuolation in the liver in males, as well as urinary bladder histopathology in both sexes.

Rat

- The PWG review of the hemangiomatous tumors in Wistar rats concluded that the incidence of benign and malignant hemagiomatous tumors were not treatment-related. The CARC concurred with this decision.
- *Adequacy of Dosing:* The high dose was considered adequate for testing the carcinogenic potential of metam sodium in rats, based on the decreases in body weight gain, food efficiency, and macroscopic and microscopic pathology observed in both sexes in this study.

2. Mutagenicity

- There is no mutagenic concern for metam sodium.

3. Structure Activity Relationship

- Metam sodium, dazomet and MITC are related to each other by virtue of the metabolism of metam sodium and dazomet to MITC. All three metabolize to CS_2.

4. Mode of Action

- No mode of action data were submitted for this chemical.

VI. CLASSIFICATION OF CARCINOGENIC POTENTIAL

In accordance with the *EPA's Final Guidelines for Carcinogen Risk Assessment* (March, 2005), the CARC classified Metam Sodium as **"Likely to be Carcinogenic to Humans"**. This was based on a treatment-related increase in malignant angiosarcomas in both male and female mice, which exceeded both the range and means of historical controls in both sexes, and had a high incidence in males (up to 52%). No treatment-related tumors were seen in rats. There is no mutagenic concern for metam sodium. No mode of action data were submitted for this chemical.

VII. QUANTIFICATION OF CARCINOGENIC POTENTIAL

In 1995, the CPRC recommended that for the purpose of risk characterization, a low dose extrapolation model be applied to the animal data for the quantification of human risk (Q_1*), based on the total incidence of angiosarcomas in male mice, at all sites combined. Based on the current "Likely" classification, the quantification of risk is still required.

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